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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/771,208	01/26/2001	Juan F. Medrano	407T-923710US	7351

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Tom Hunter
SKJERVEN MORRILL MacPHERSON LLP
Suite700
25 Metro Drive
San Jose, CA 95110-1349

EXAMINER	
SHUKLA, RAM R	
ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/771,208	MEDRANO ET AL.	
	Examiner	Art Unit	
	Ram R. Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-76* is/are pending in the application.

4a) Of the above claim(s) *1-7,23-26 and 37-76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *8-22 and 27-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 January 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election of the invention of group II, claims 8-22 and 27-36 in Paper No. 10, filed 11-7-02 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1-7, 23-26 and 37-76 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 10. It is noted that claim 8 encompasses the inventions of the groups II and III. It will be examined to the extent it encompasses the invention of group II, the elected invention.

3. Claims 8-22 and 27-36 are under consideration.

Specification

4. The disclosure is objected to because of the following informalities:

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code at several places, for example, on page pages 72 (line 12) and page 73 (line 31). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. Applicants are required to check the entire specification for any other hyperlinks and correct them.

Appropriate correction is required.

5. The references 2-6 of the information disclosure statement filed 8-29-02 has been placed in the application file, but the information referred to therein has not been considered because these references are Genbank sequence listing and their relevance to the instant application is not clear. The applicants did not provide any statement as to how are these references relevant to the instant invention.

Claim Objections

6. Claim 11 is objected to because of the following informalities: The word "as" before neo in line should be "a". Appropriate correction is required.

7. Claims 8-22 and 27-36 are objected to because they have not used the term Socs2 or SOCS2 consistently. Appropriate correction is required.

8. Claim 29 is objected to because of the following informalities: the word "wherein" has been repeated in line 1. Appropriate correction is required.

Claim Rejections - 35 USC § 101

9. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

10. Claims 12-22 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Instant claims recite a knockout mammal that will encompass a human, a non-statutory subject. Use of the term "a knockout non-human mammal" will obviate the rejection.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 11-22 and 27-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant is referred to the revised interim guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, page 1099-111 (also available at www.uspto.gov).

Claimed invention is drawn to any knockout mammal wherein the level of Socs2 protein in decreased due to disruption of Socs2 gene. Claim 11 is drawn to a method in which a selectable marker is a cDNA.

The specification provides prophetic examples of the methodology to make transgenic animals and knockout animals. The specification also teaches a transgenic homozygous knockout mouse in which both the alleles of the Socs2 gene have been disrupted resulting in the loss of Socs2 protein and the mouse grew larger than its wild type littermates (see specification on page 74, lines 19-32 and pages 75-76). There is no guidance the structure of any other knockout animal except the mouse.

In analyzing whether the written description requirement is met, it is first determined whether the whether a representative number of species have been described by their complete structure. Since it is not realistic to expect that the "complete structure" of any transgenic animal, or even a cell, could be described, this requirement is interpreted to be whether phenotypic consequences or other characteristics of the animals resulting from altering the genotype have been described. In the instant case, the claimed invention invention encompasses knockout animals in which the expression of the recited gene is either inhibited or completely eliminated or heterozygous animal in which only one allele of the gene is disrupted. Considering the fact knockout animals is highly unpredictable, the structure of the animals and phenotype of the genus of animals encompassed by the broad claim cannot be predicted. The art teaches that phenotype of a transgenic mouse cannot be predicted. Wood (Comparative Medicine 50 (1): 12-15, 2000) noted:

"The phenotype of an animal is determined by a complex interaction of genetics and environment. It is the evaluation of the phenotype that allows us to determine the usefulness of a mutant strain as a model for biomedical research.....A specific phenotype is usually expected from genetically altered mice whether they

are transgenic over-expression models or gene knockout models where a particular gene function has been modified or ablated altogether. Thus for any given genetic alteration, we often try to predict what the phenotype will be. Many times we find the predicted phenotypes or more. It is, however, common to hear that surprisingly a given model has "no phenotype"."

This clearly indicates that the phenotype of a transgenic animal cannot be predicted. Therefore, the specification does not describe the phenotype of a representative number of species of the genus. Regarding claim 11, it is noted that the specification does not teach the structure of a cDNA that will be used in the method or what is the sequence structure of the representative number of species of the genus of cDNA.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. In case of a knockout animal, it is not possible to adequately describe the claimed animals because the effects of inactivating a gene cannot be predicted, particularly when a gene product may be interacting with the proteins of a family of proteins. For example, Korach et al (US Patent No. 5,650550) produced a knockout mouse lacking a functional estrogen receptor. One skilled in the art would not have predicted that such an animal would even be viable (see col 9, lines 22-39), much less have been able to predict the resulting phenotype. In the instant application, what would have been the result of the inactivating or inhibiting Socs2 gene cannot be predicted in the transgenic animals encompassed by the invention. It is noted that even if one has made a transgenic mouse for a gene using certain construct, the phenotype of other species of knockout or transgenic animals can not be predicted, due to the factors of unpredictability of site of integration, copy number of the transgene integrated etc. For example, Hammer et al (Hammer RE et al. Cell 63:1099-1112.1990) created both transgenic mice and rats expressing human HLA-b27 gene and beta-2 microglobulin. Although, both the transgenic animals bearing HLA-27 gene expressed the gene, transgenic mice did not show any HLA-2 associated disease whereas the transgenic rats demonstrated most of the HLA-B27 related diseases (see lines 20-28 in col 2 of page 1099). This shows that the

integration of a transgene into alternative species may result in widely different phenotypic responses even in animals of the same species. Additionally, promoters and enhancer elements may not function in all the species because they may require specific cellular factors. In summary, with the limited information disclosed in the specification, an artisan would have not been able to predict whether all these animals would have had same or different phenotypes compared to the knockout mice or transgenic mice. Again regarding claim 11, the specification does not teach the identifying characteristics of the representative number of species of cDNA.

Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Therefore, the limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the huge genera recited in the claims at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genera.

13. Claims 8-22 and 27-36 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a homozygous knockout mouse wherein both the alleles of the endogenous Socs2 gene in the genome of the mouse have been disrupted by inserting an expression cassette and wherein the knockout mouse is characterized by a large size and increased body weight and lack of

functional Socs2 protein and a method of producing the knockout mouse, does not reasonably provide enablement for the other recited embodiments. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

As the current state of the transgenic animal research stands, there are several significant limitations to the application of same methodology of making transgenic animals to different species. Longer gestation times, reduced litter sizes, number of fertilized eggs required for micro injection and relatively low efficiency of gene integration and method of introduction of transgenes are a few examples of such limitations. Introduction of foreign DNA into fertilized oocyte , for example by micro injection, may result in random integration of the exogenous DNA into host chromosomal DNA which in turn may have major consequences on the expression of the transgene, therefore the production of transgene in all the

non-human mammals species will be highly variable and unpredictable. Even if the transgenic animals are produced, it is highly unpredictable whether transgenic animals from species other than mouse (in the present case) will express the transgene to a level high enough so as to enable the development of the claimed phenotype in the transgenic animals.

In an assessment of the transgenic technology at the time of the invention, Cameron (Cameron ER. Molecular Biotechnology 7:253-265, 1997) noted, " Well regulated transgene expression is the key to successful transgenic work, but all too often experiments are blighted by poor levels or the complete absence of expression, as well as less common problems, such as leaky expression in nontargeted tissues. A feature common to many transgenic experiments is the unpredictable transgenic lines produced with the same construct frequently displaying different levels of expression. Further, expression levels do not correlate with the number of transgene copies integrated. Such copy- number-independent expression patterns emphasize the influence of surrounding chromatin on the transgene" (see page 256, section 4 on transgene regulation and expression).

The art of culturing and maintaining ES cells in culture is unpredictable. Gardner and Brook (Gardner RL and Brook FA. International J. of Dev. Biol. 41:235-243, 1997) summarized the progress in the field of ES cell biology, "Remarkably little is known about mammalian embryonic stem (ES) cells despite their very widespread use in studies on gene disruption and transgenesis. As yet, it is only in the mouse that lines of ES cells which retain the ability to form gametes following reintroduction into the early conceptus have been obtained. Even in this species, most stains have so far proved refractory to the derivation of cell lines....." Additionally, gene targeting and selection of the ES cells that harbor the integration of a desired construct also has been shown to be unpredictable in animals other than mice. To prevent their differentiation, ES cells are maintained in culture in the presence of mouse derived factors that inhibit differentiation either by coculturing the cells in the presence of feeder cell lines or by adding agents to the culture as a media supplement. However, it has been suggested that the such differentiation-

inhibitory derived from mouse do not adequately prevent differentiation of stem cells in species other than the mouse.

The steps of producing a knockout mouse that include, isolating the gene from a mouse genomic library, destroying the gene by inserting therein a selectable marker gene, introducing vectors incorporated with the destroyed gene into cultured ES cells thereby allowing homologous recombination to occur, isolating and identifying a clone in which homologous recombination has been effected, injecting the clone into a blastocyst that develops into the desired mouse. While the steps to produce knock out mouse have been well developed and used in mice, they have not been fully developed in other animals, particularly the art of gene targeting in ES cells and culture and selection of the ES cells that harbor the desired integration has been shown to be unpredictable in animals other than mice (as discussed above. It was recognized in the art at the time of the invention production of species other than mouse has not been successful

It is noted that the invention as claimed encompasses method of producing any animal characterized by inhibiting expression of a Socs2 gene or hy disrupting gene by homologous recombination, any knockout mammals in which Socs2 gene is disrupted and the mammal is homozygous or heterozygous. It is noted that in view of the unpredictability of the state of the art of making knockout and transgenic animals as discussed above and in view of the lack of the teachings to address the art recognized problems and issues in transgenesis, an artisan of skill would have required extensive experimentation to make and use the claimed invention and such experimentation would have been undue due to the unpredictability of the art and lack of the guidance in the art and in the specification.

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, one of ordinary skill in the art at the time of the invention would have required an undue amount of experimentation to make and use the claimed invention commensurate with the full scope of the claims. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714

(BPAI 1991). Accordingly, limiting the scope of the claimed invention to a homozygous knockout mouse wherein both the alleles of the endogenous Socs2 gene in the genome of the mouse have been disrupted by inserting an expression cassette and wherein the knockout mouse is characterized by a large size and increased body weight and lack of functional Socs2 protein and a method of producing the knockout mouse is proper.

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 8-22 and 27-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8 and 13 are vague and indefinite because it is unclear as to what is meant by the term "a high growth phenotype". The metes and bounds of the term are not defined.

Claim 9 recites the limitation "said Socs2 gene" in line 3. There is insufficient antecedent basis for this limitation in the claim because it is unclear as to which Socs2 gene the term is referring to- one in claim 8 or the one in claim 9.

Claims 12, 30 and 31 is vague and indefinite because it is unclear as to what is meant by the term "said mammal comprising cells containing a .....".

Claim 17 is vague and indefinite because it is unclear as to what is meant by "disruption comprising an expression cassette".

16. No claim is allowed.

17. Inventor's article (Nature 405:1069-1073, 2000) is noted as it describes a Socs2 knockout mouse.

When amending claims, applicants are advised to submit a clean version of each amended claim (without underlining and bracketing) according to § 1.121(c).

For instructions, Applicants are referred to http://www.uspto.gov/web/offices/dcom/olia/aipa/index.htm.

Applicants are also requested to submit a copy of all the pending/under consideration claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the William Phillips whose telephone number is (703) 305-3413.

RAM R. SHUKLA, PH.D
PATENT EXAMINER

Ram R. Shukla, Ph.D.
Primary Examiner
Art Unit 1632